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EXAMINER	
GAMBEL, PHILLIP	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/435992	Applicant(s) HANNA
	Examiner GAMBEL	Art Unit 1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/24/01

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 60-85

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 60-85

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 9/4/01 (Paper No. 17), has been entered.
Claims 42-56 have been canceled.
Claims 57-59 have been added.

2. Applicant's election of Group I as it reads on the combination of anti-CD40L antibody and anti-CD20 antibody and leukemia as the $CD40^+$ malignancy in Paper Nos. 11 and 17 is acknowledged.

Applicant further elects ^{90}Y and alkylating agents as the chemotherapeutics in combination with the elected species.

Given the cancellation of Group II, the restriction between Groups is rendered moot.

Although applicant has still clearly indicated whether they have elected radiolabel or non-radiolabeled anti-CD40L antibody and/or anti-CD20 antibody; the following Office Action is set forth in the interest of compact prosecution.

For the purposes of this Office Action, the anti-CD20 antibody is radiolabeled (e.g. ^{90}Y) and anti-CD40L antibody is not radiolabeled.

This election of an anti-CD20 antibody which is radiolabeled (e.g. ^{90}Y) and an anti-CD40L antibody which is not radiolabeled appears consistent with the Examples set forth in the instant specification and the election of leukemias rather than lymphomas.

Although applicant did not point which claims read on the elected invention, claims 3-5, 14-17 , 28-31 and 36-41 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to nonelected species.

Claims 1, 2, 6-13, 18-27, 32-35, 57-59 are under consideration in the instant application, as they read on the elected invention/species.

3. No information disclosure statement has been filed with this application.

4. Although the specification discloses a Brief Description of Drawings, no Figures appear with the instant application. After this Office Action is mailed, it will be sent to the Office of Petitions with respect to the missing Figures.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10-13, 18-27, 32-35, 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "CD20-specific antibodies which are radiolabeled" (as the elected invention) (or CD40-specific antibodies which are radiolabeled", which was not elected) and "antigen binding fragments thereof" does not reasonably provide enablement for any "second antibody" or "fragment thereof"
The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Again, for the purposes of this Office Action, the anti-CD20 antibody is radiolabeled (e.g. ^{90}Y) and anti-CD40L antibody is not radiolabeled.

Applicant has not provided sufficient direction and guidance as to any "second" other than "CD20-specific antibodies which are radiolabeled" (as the elected invention) (or CD40-specific antibodies which are radiolabeled", which was not elected) and antibody fragment thereof"' that would retain the specificity and function of the "CD20-specific (or CD40-specific) antibody, encompassed by the claimed methods.

While a "second antibody" and "fragment thereof" may have some notion of the activity of the claimed agents to be used in the claimed methods; there is insufficient direction and guidance as to the structural nature or properties to enable any "second antibody" or "fragment thereof" to treat leukemia (or non-elected lymphoma). For example, antibodies encompass a broad and diverse set of specificities and the skilled artisan would not predict that any "second antibody" would be appropriate for targeting or treating leukemia (or lymphoma).For example, such "fragments" could read on an Fc portion of an immunoglobulin or modified antibody fragments that do not bind CD20 (or CD40) and would not be predictive to target the appropriate cells (or to block the appropriate (receptor:ligand interactions).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "second antibody" or "fragment thereof" other than those that bind CD20 (or CD40) to target and/or treat leukemia (or lymphoma).

8. Claims 7-10, 12-13, 18-21, 33, 35, 57:

It is apparent that IDEC-131, 3E4, 2H5, 2H8, 4D9-8, 4D9-9, 24-31, 24-43, 89-76 or 89-79 as well as the RITUXAN and B1 antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that certain of these antibodies are claimed in U.S. Patents (e.g. see art rejections below) which would be indicative, but not necessarily mean (see MPEP 2404.01) that the enablement of biological materials under 35 USC, 112, first paragraph, has been satisfied.

Applicant is required to indicate which antibodies are enabled accordingly and to satisfy the deposit of the biological materials for the others accordingly.

9. Claim 59 is objected to because "trating" should be "treating"

10. Claim 7-13, 21, 35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 7-10, 12-13, 18-21, 33, 35, 57: "IDEC-131, 3E4, 2H5, 2H8, 4D9-8, 4D9-9, 24-31, 24-43, 89-76 or 89-79 as well as the RITUXAN and B1" are indefinite in the recitation of these "designations" because their characteristics are not known. The use of these "designations" as the sole means of identifying the claimed antibodies renders the claims indefinite because these are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines .

Amending the claims to recite the appropriate ATCC Accession Numbers would obviate this rejection.

B) Claims 7-10, 12-13, 21, 35: contain the trademark or trade name "RITUXAN" and "IDEC-131" Where a trademark or trade name is used in a claims as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 USC 112, second paragraph, See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark or the trade name "RITUXAN" or "IDEC-131" is used to identify or describe an antibody, and accordingly, the identification or the description is indefinite. The relationship between a trademark or tradename and the product it identifies may be uncertain and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark or tradename.

C) Claims 11-13 are indefinite in that they do not define the radiolabeled antibody (or radilabeled anti-CD20 antibody) as the "second antibody" of the claim 10 (and elected invention).

D) Claim 21 is indefinite in that it depends upon itself.

For examination purposes, claim 21 is interpreted to be dependent upon claim 20.

E) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 2, 6-13, 18-27, 32-35, 57-59 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kaminski et al. (U.S. Patent No. 6,287,537) AND/OR Anderson et al. (U.S. Patent No. 5,843,439) in view of Smiers et al. (Br. J. Haematol. 93: 125-130, 1996), Schattner et al. (Blood 91: 2689-2697, 1998), Gruss et al. (Leukemia and Lymphoma 24: 393-422, 1997), Renard et al. (Blood 87: 5162-5170, 1996), Black et al. (U.S. Patent No. 6,001,358), Noelle et al. (U.S. Patent No. 5,747,037) in view of standard chemotherapeutic treatments, including combination therapy of leukemias known and practiced by the ordinary artisan at the time the invention was made, as acknowledged on pages 39-40 of the instant specification.

Kaminski et al. teach the use of anti-CD20 antibodies, including radiolabeled anti-CD20 antibodies (e.g. B1) in combination with other treatments to treat B cell malignancies (see entire document, Summary of the Invention and Detailed Description of the Invention). Kaminski et al. teach the art known expression of CD20 on B cell leukemias (column 4, paragraph 1).

Anderson et al. teach the use of anti-CD20, including radiolabeled anti-CD20 antibodies (e.g. 2B8 / RITUXAN) in cooperative strategies to treat B cell malignancies (See entire document). Anderson teach that the anti-CD20 antibody 2B8 was raised against the human acute lymphoblastic line SB (column 12, 2B8).

Therefore, the prior art taught combination therapy to various B cell malignancies, including B cell leukemias with radiolabel CD20-specific antibodies, including B1 and RITUXAN at the time the invention was made. Both references teach the use of art known radiolabels including ^{90}Y for radioimmunotherapeutic antibodies (see entire documents), encompassed by the claimed methods. Therefore, the claimed labels (e.g. claim 13) were known and routinely practiced at the time the invention was made.

The references do not teach the use of radiolabeled CD20-specific antibodies in combination with CD40L-specific antibodies.

Smiers et al. teach that is was known at the time the invention was made that B cell leukemias expressed both CD20 and CD40 and leukemic cells proliferate in response to either CD20 or CD40 activation (see entire document, including Discussion).

Schattner et al. teach that CD40L is expressed on certain chronic lymphocytic leukemias and is important factor in CLL tumor growth as well as an important factor in the generation of pathologic antibody in some patients with CLL (see entire document, including Abstract and Discussion). Schattner et al. also teach that is was known at the time the invention was made that B cell leukemias expressed both CD20 and CD40 (see Abstract).

Gruss et al. teach that CD40 is expressed on B cell leukemias and that the CD40:CD40L pathway, including CD40L-expressing T cells, which are readily detectable around neoplastic B cells, enhance B cell activation and growth (see pages 404-405, B cell Lymphomas and Lymphoproliferative Disorders). It is noted that Gruss et al. teach the therapeutic use of recombinant CD40L rather than CD40L-specific antibodies as inhibitors of malignant B cell growth (page 404, column 1). While Gruss et al. disclose the art known formation of neutralizing anti-mouse antibodies as a limitation of antibody therapy, such limitations have been long addressed by the use of recombinant antibodies such as humanized antibodies, known and practiced in the art for a decade (also, see Noelle et al. and Black et al. herein).

Renard et al. teach autologous CD4+ T cells isolated from leukemia patients were able to induce CD40-dependent proliferation of B cell leukemic blasts (see entire document, including the Abstract). Also, this proliferative response was inhibited by anti-CD40L antibody (see Results).

Therefore, the prior art of Schattner et al., Gruss et al. And Renard et al. taught the importance of CD40L-mediated interactions in B cell leukemia and clinical manifestation. Also as pointed out above, Gruss et al. does teach that CD40:CD40L interactions are par of cellular activation and neoplastic tumor cell growth which would be useful for the therapeutic management of $CD40^+$ tumors (see page 404, column 1).

Gruss et al. does not teach the art known CD40L-specific antibody antagonists, including the antibody species encompassed by the claimed invention.

Black et al. teach the use of gp39/CD40L-specific antibodies, including recombinant antibodies and antibody fragments, to inhibit CD40:CD40L interactions or where gp39 inactivation and/or modulation of the gp39(CD40L)/CD40 interaction is desirable (e.g. column 11, lines 34-39 and column 14, lines 35-38). (see entire document, including Summary of the Invention and Detailed Description of the Invention). In addition, Black et al. teach the antibody species 24-31, encompassed by the claimed invention (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims).

Noelle et al. teach gp39- /CD40L-specific antibodies (e.g. see column 3, paragraph 3 and column 4, paragraph 2) encompassed by the claimed invention (e.g. claim 7), which are useful for in inhibiting the interaction between gp39/CD40L with its ligand CD40 (see entire document, including Summary of the Invention and Detailed Description of the Invention). In addition, Noelle et al. teach the art known use of recombinant antibodies and antibody fragments (e.g. see gp39 Antagonists, column 6-9), encompassed by the claimed invention (e.g. claims 8 and 9).

Black et al. and Noelle et al. both teach the art known advantages of recombinant antibodies and antibody fragments as therapeutic agents (see Detailed Description of the Invention), given their decreased immunogenicity compared to their native murine antibody counterparts and ease of production and homogeneity.

The instant specification acknowledges standard chemotherapeutic treatments of leukemias, including combination therapy was known and practiced by the ordinary artisan at the time the invention was made (see pages 39-40 of the instant specification). Therefore, the chemotherapeutic agents including the alkylating agents employed in the claimed methods was obvious, given their standard use by the ordinary artisan at the time the invention was made.

Given the teachings of Kaminksi et al. to employ radiolabeled antibodies in combination with other treatments to treat leukemia as well as the acknowledgment by applicant that combination therapy was known and practiced in the art at the time the invention was made, one of ordinary skill in the art would have been motivated to treat B cell leukemia with a combination of therapies.

Given the expression of CD20 and CD40 and the ability of activation via CD20 and/or CD40, the ordinary artisan would have been motivated to target B cell leukemia directly with radiolabeled CD20-specific antibodies and to diminish activation of said B cell leukemia by blocking activation with CD40L-specific antibodies.

One of ordinary skill in the art would have employed non-radiolabeled CD40L-specific antibodies, given the expression of CD40L on normal activated T cells and the role of such CD40L on such T cells to stimulate CD40-expressing B cell leukemic cells, as taught above.

Radiolabeled CD40L-specific antibodies would target and kill non-malignant T cells.

Also, Schattner et al. teach that the CD40L expressed on certain B cell leukemic cells played a role in B cell leukemic and autoimmune manifestations in leukemia patients.

Also as pointed out above, Gruss et al. does teach interrupting CD40:CD40L interactions to inhibit tumor cell activation and growth.

Given the standard regimen of chemotherapy in leukemic patients and the teachings of Kaminski et al. to combine standard therapy with radiolabeled antibodies, one of ordinary skill in the art at the time the invention was made to employ multiple modalities to treat B cell leukemia. Given the addition of non-radiolabeled CD40L-specific antibodies, the ordinary artisan would have been administering a less toxic therapeutic regimen, when compared to radiolabeled antibodies and chemotherapeutic agents.

One of ordinary skill in the art at the time the invention was made would have been motivated to select radiolabeled CD20-specific antibodies, non-radiolabeled CD40L-specific antibodies and standard chemotherapeutic to treat B cell leukemia at the time the invention was made, given the teachings above. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1, 2, 6-13, 18-27, 32-35, 57-59 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over pending claims of copending applications USSNs 09/772,938 and 09/834,933 . Given the election in the instant case, the conflicting claims may or may not be identical, depending upon the invention(s) elected in these copending applications. The claims are not patentably distinct from each other because they appear to read on the same or nearly the same reagents to treat the same or nearly the same leukemias and lymphomas.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

Phillip Gambel, PhD.
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November 19, 2001